Uremic encephalopathy

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Uremic encephalopathy encompasses a wide range of central nervous system abnormalities associated with poor kidney function occurring with either progressive chronic kidney disease or acute kidney injury. The syndrome is likely caused by retention of uremic solutes, alterations in hormonal metabolism, changes in electrolyte and acid-base homeostasis, as well as changes in vascular reactivity, blood–brain barrier transport, and inflammation. There are no defining clinical, laboratory, or imaging findings, and the diagnosis is often made retrospectively when symptoms improve after dialysis or transplantation. The diagnosis is also made difficult because of the many confounding and overlapping conditions seen in patients with chronic kidney disease and acute kidney injury. Thus, institution of kidney replacement therapy should be considered as a trial to improve symptoms in the right clinical context. Neurological symptoms that do not improve after improvement in clearance should prompt a search for other explanations. Further knowledge linking possible uremic retention solutes with neurological symptoms is needed to better understand this syndrome as well as to develop more tailored treatments that aim to improve cognitive function.

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Uremic encephalopathy is an ill-defined and complex syndrome of cognitive and nervous system dysfunction seen in patients with acute or chronic kidney disease (CKD) that is often accompanied by nonneurological symptoms. Although there is no consensus definition of this syndrome, the major defining characteristics are listed in Table 1. The diagnosis is often one of exclusion and validated only with improvement in cognitive function and symptoms with institution of kidney replacement therapy (KRT).

It is important to distinguish the relatively quickly developing syndrome of uremic encephalopathy from other forms of cognitive dysfunction in CKD and end-stage kidney disease that typically evolve over extended time periods and at best only partially improve with increased clearance of putative neurotoxins.[1] Indeed, epidemiological studies have shown that cognitive impairment may already be common in relatively early stages of CKD to become more prevalent as glomerular filtration rate (GFR) falls.[2–5] In 1 study, moderate CKD, reflected by estimated GFR 30 to 59 ml/min per 1.73 m^2, was significantly associated with poorer performance in visual attention and learning/concentration.[6]

EPIDEMIOLOGY

The lack of clear defining features of uremia makes data difficult to analyze.[7] However, it is likely that severe encephalopathy is an uncommon occurrence in patients with progressive CKD because most patients will start planned KRT before severe central nervous system (CNS) manifestations can occur. This may be less likely in the setting of acute kidney injury (AKI) where falls in GFR are less predictable and more rapid.[7]

CLINICAL FEATURES

Distinguishing the various forms of cerebral disease seen with CKD from those of uremic encephalopathy is difficult and is further hindered by lack of clear distinguishing clinical and laboratory findings (Table 2). Uremic encephalopathy is typified by changes in sensorium that include loss of memory, impaired concentration, depression, delusions, lethargy, irritability, fatigue, insomnia, psychosis, stupor, catatonia, seizures, and coma. History and physical examination may reveal impaired cognition but also the presence of myoclonic jerks, asterixis, dysarthria, nystagmus, papilledema, agitation,

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Table 1 | Proposed characteristics of uremic encephalopathy

Definition	• Acute or subacute toxic syndrome attributable to the accumulation of solutes that occurs with severely reduced kidney function ○ Other putative etiologies include imbalance of excitatory and inhibitory neurotransmitters in the brain, alterations in the blood–brain barrier, changes in vascular permeability, increased inflammation, and cerebral edema
Symptoms	• Cognitive and nervous system dysfunction associated with acute kidney disease or CKD ○ CNS symptoms are variable and may include loss of memory, impaired concentration, depression, delusions, lethargy, irritability, fatigue, insomnia, psychosis, stupor, catatonia, seizures, and coma ○ Other related symptoms may include peripheral neuropathies, sleep disorders, restless legs, muscle cramps, and myoclonus ○ May have associated nonneurological symptoms such as nausea, vomiting, and dysgeusia
Characteristics	• Usually manifested when GFR is <15 ml/min per 1.73 m^2 or seen in patients with kidney failure who are receiving inadequate dialysis ○ Symptoms may be milder and more insidious with slowly progressive CKD ○ Symptoms are more severe when the fall in GFR is acute • No definitive characteristic imaging or EEG findings • Symptoms are independent of the etiology of kidney failure • Substantial overlap with other conditions. Diagnosis of exclusion with the key distinguishing feature being improvement with the initiation of dialysis, increase of dialysis clearance, or transplantation

CKD, chronic kidney disease; CNS, central nervous system; EEG, electroencephalogram; GFR, glomerular filtration rate.

Table 2 | Possible confounding medical conditions

Etiological category	Conditions
Noninfectious	• Cerebrovascular disease ○ Atheromatosis ○ Atherosclerosis ○ Vasculitis • Metabolic conditions ○ Diabetes mellitus ○ Hypoglycemia ○ Hyperglycemia ○ Ketoacidosis ○ Lactic acidosis • Hypertension • Hypotension • Hyperparathyroidism • Liver failure • Autoimmune diseases • Trauma • Withdrawal states (e.g., ethanol and benzodiazepines) • Electrolyte disturbances ○ Hyponatremia ○ Hypernatremia ○ Acidosis
Infectious diseases	• Viral (e.g., herpes encephalitis) • Bacterial ○ Sepsis ○ Systemic inflammatory response syndrome (SIRS) • Malaria • Leptospirosis
Neurotoxic	• Psychotropic drugs (e.g., antidepressants and antipsychotics) • Recreational drugs (e.g., stimulants, depressants, and hallucinogens) • Solvents • Mushroom poisoning • Drugs that are not directly targeting the nervous system ○ Antibiotics (e.g., metronidazole, quinolones, penicillins, and cephalosporins) ○ Antimycotics (e.g., voriconazole and amphotericin B) ○ Antimycobacterials (e.g., isoniazid)

tetany, seizures (typically, tonic-clonic), and coma. Patients may also present with slurred speech, pruritus, muscle twitches, or restless legs along with gastrointestinal symptoms such as nausea and vomiting. Other symptoms indicative of severely reduced GFR such as fluid retention may also be present. Laboratory work typically reveals characteristic findings of kidney failure with elevation in serum creatinine and blood urea nitrogen (BUN) along with metabolic acidosis and hyperkalemia. Anemia is also common and can contribute to worsening cognitive function.[3]

In patients with severe AKI, encephalopathy typically occurs within days of the fall in GFR.[8] Of note, with recent evidence that early initiation of KRT in AKI does not result in better survival over dialysis initiation based on the classical criteria, we may see an increase in uremic encephalopathy symptoms as patients may be exposed longer to a significant loss of GFR.[9] In patients with CKD or underdialyzed patients with end-stage kidney disease, the onset of uremic encephalopathy may be more insidious (weeks or months) and thus may remain unrecognized until more severe cognitive dysfunction is present. Multiple dialysis sessions may be required to see maximum benefit. Residual neurological symptoms that persist after dialysis initiation more likely represent the effect of irreversible neurological disease or other comorbid conditions.

PATIENT EVALUATION

Clinical

The key elements of the evaluation of patients with suspected uremic encephalopathy are to exclude other etiologies of encephalopathy, determine the severity of the neurological changes, and assess the need for urgent or emergent dialysis. In patients with a slow decline in GFR (such as with progressive CKD), symptoms such as fatigue, anorexia, weight loss, and nausea are most predominant. Development of cognitive dysfunction in these patients may be slow, progressive, and subtle and may require a specific psychometric study for detection. Sleep disorders, including reduction in total sleep time, insomnia, daytime somnolence, altered circadian rhythm, sleep apnea, and restless legs syndrome, are also very common.[1,2] At the other end of the spectrum are patients with a rapid decline in GFR usually in the setting of AKI. These patients can

present with more severe symptoms of confusion, delirium, seizures, and coma.

Laboratory evaluation

Laboratory evaluation is focused on the determination of the serum creatinine, BUN, serum electrolyte, and glucose concentrations; acid-base status; and complete blood count, supplemented with toxicology laboratory screening or medication levels when clinically indicated. Determination of estimated GFR is useful in steady-state conditions. A long-standing debate in clinical practice has centered on whether there are specific BUN levels that make the diagnosis of uremic encephalopathy more likely and prompt initiation of dialysis, whereby the practice of targeting urea clearance values (Kt/V) for dialysis has caused an overreliance on BUN values. BUN levels are not well correlated with symptoms such as encephalopathy.[10,11] A classic study showed that severe uremic symptoms including signs of encephalopathy did not increase in patients on hemodialysis when urea was added to the dialysate to maintain the BUN level at ~150 to 300 mg/dl.[11] More recently, targeting dialysis prescriptions to higher urea clearances in the Effect of Dialysis Dose and Membrane Flux in Maintenance Hemodialysis study demonstrated no clear benefit although specific data on changes in CNS function was not provided.[12] Other studies demonstrated no association between the adequacy of dialysis as measured by urea kinetics (Kt/V) and cognitive function in patients undergoing chronic hemodialysis.[13–16] Thus, caution should be exercised in attributing encephalopathic symptoms to a specific cutoff value of BUN and BUN is an imperfect marker for the risk of uremic encephalopathy. Of note, in an experimental study in mice, doubling urea concentration with intact kidney function induced several features of depression via interruption of long-term potentiation, inhibition of the mTORC1-S6K pathway, and possibly cabarmoylation.[17] The study however does not refer to encephalopathy or cognitive dysfunction, leaving the question regarding the role of urea in uremic encephalopathy essentially open.

Imaging and other techniques

Imaging of the CNS with either computed tomography or magnetic resonance imaging (MRI) is most useful to exclude other etiologies of encephalopathy and should be obtained if patients have focal neurological deficits. In most cases of uremic encephalopathy, imaging is normal or shows nonspecific findings. Case reports describe isolated cortical, centrum semiovale, basal ganglia, and brainstem involvement revealed by MRI.[18] The lentiform fork sign on MRI that consists of bilateral symmetrical hyperintensities in the basal ganglia surrounded by a hyperintense rim delineating the lentiform nucleus has been seen in patients with uremic encephalopathy (Figure 1).[18–20] However, this finding is also encountered in patients with metabolic acidosis from any cause as well as in the dialysis disequilibrium syndrome and thus is neither sensitive or specific for uremic encephalopathy.[21,22] Electroencephalograms are of limited value and generally show generalized slowing. However, with a more acute evolution, irregular low voltage with slowing of the posterior dominant alpha rhythm and occasional theta bursts and prolonged bursts of bilateral, synchronous slow and sharp waves or spikes and waves are present. Rarely, generalized or partial seizure activity may be encountered.[23]

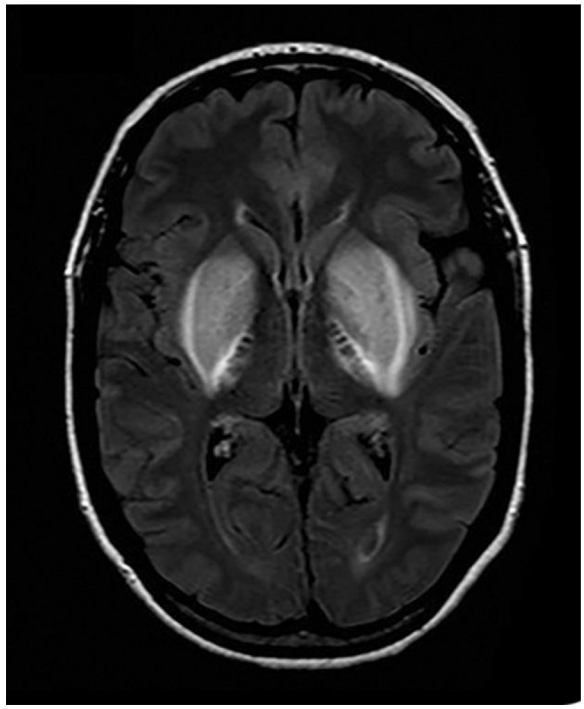

Figure 1 | Lentiform fork sign on brain magnetic resonance imaging (MRI). Brain MRI reveals a pattern of vasogenic edema with T2/fluid-attenuated inversion recovery hyperintensity in the basal ganglia compatible with the lentiform fork sign. Reprinted with permission from Wolters Kluwer Health, Inc., Fernandes GC, Koltermann T, Campos L, Vedolin L, Rieder CRM. Teaching NeuroImages: the lentiform fork sign: an MRI pattern of metformin-associated encephalopathy. *Neurology*, volume 84, issue 3, e15. https://n.neurology.org/content/84/3/e15.long. © 2015 American Academy of Neurology.[20]

A critical question is whether any tests of CNS function can reliably detect changes associated with uremia and document reversal of these changes with the institution of KRT. There are scant data on this issue, and complicating features include the effects of dialysis itself on CNS function as well as comorbid conditions. In addition, the lack of specific diagnostic criteria for uremic encephalopathy makes comparisons difficult. In 1 study that used transcranial magnetic stimulation, investigators noted that before the institution of dialysis, patients demonstrated alterations in cortical excitability that could be reversed once hemodialysis was started.[24] The researchers attributed these changes to changes in osmolality that occurred with dialysis. More research is needed to better document serial changes in brain function in patients with end-stage kidney disease.

PATHOPHYSIOLOGY OF UREMIC ENCEPHALOPATHY

The pathophysiology of uremic encephalopathy is complex and multifactorial and remains poorly understood (Figure 2). The underlying driver is impaired kidney function that leads to retention of metabolites, alterations in hormonal metabolism, changes in electrolyte and acid-base homeostasis, as well as changes in vascular reactivity, blood–brain barrier (BBB) transport, and inflammation. These various effects interact to impact CNS function.

Uremic toxins

Uremic retention solutes or uremic toxins have been linked to neurotoxicity (Table 3).[25] According to previous and updated definitions, plasma, serum, or blood concentrations should be increased in CKD versus normal kidney function to accept a solute as toxin and ideally concentrations of these substances should be linked to symptoms associated with the uremic state. In what follows, we discuss the solutes with the most compelling evidence as contributing to uremic encephalopathy.

Guanidino compounds. Guanidines, especially creatinine, guanidine, guanidino succinic acid, and methylguanidine, have been related to neuroexcitation and impaired cognition and disturbed exploratory social behavior.[26–30] These effects are mediated by the inhibition of whole cell currents evoked by γ-aminobutyric acid, activation of glycine receptors, and/or activation of ion channels associated with the *N*-methyl-D-aspartate receptor.[27,31] In addition, guanidino acetate affects the memory of rodents via inhibition of sodium-potassium adenosine triphosphatase and asymmetric dimethyl arginine in clinical studies has been associated with depression and cognitive disturbances.[32–34]

Advanced glycation end products. Advanced glycation end products are proteins or lipids that become glycated as a result of exposure to the carbamyl group of reducing sugars. Advanced glycation end products have been associated with dose-dependent death of cortical neuron cells, extension of the size of cerebral infarct lesions, and, via interaction with receptors for advanced glycation end products, cognitive functional decline.[35–37] The development of such changes is gradual rather than rapid.

Tryptophan metabolites. *Indoxyl sulfate.* The role of the indole indoxyl sulfate as an activator of pro-inflammatory, prothrombotic, and profibrotic mechanisms has extensively been studied and documented.[25,38] However, several data also suggest neurotoxicity. Intraperitoneal administration of indoxyl sulfate to uninephrectomized mice resulted in mood disorders, suggesting neurodegeneration. These were linked to functional changes in neuronal cells and neuroinflammation.[39] Indoxyl sulfate also induced apoptosis of astrocytes via oxidative stress and protein kinase inhibition.[40] Indoxyl sulfate administration to rats with CKD impaired cognitive function and BBB integrity via aryl hydrocarbon

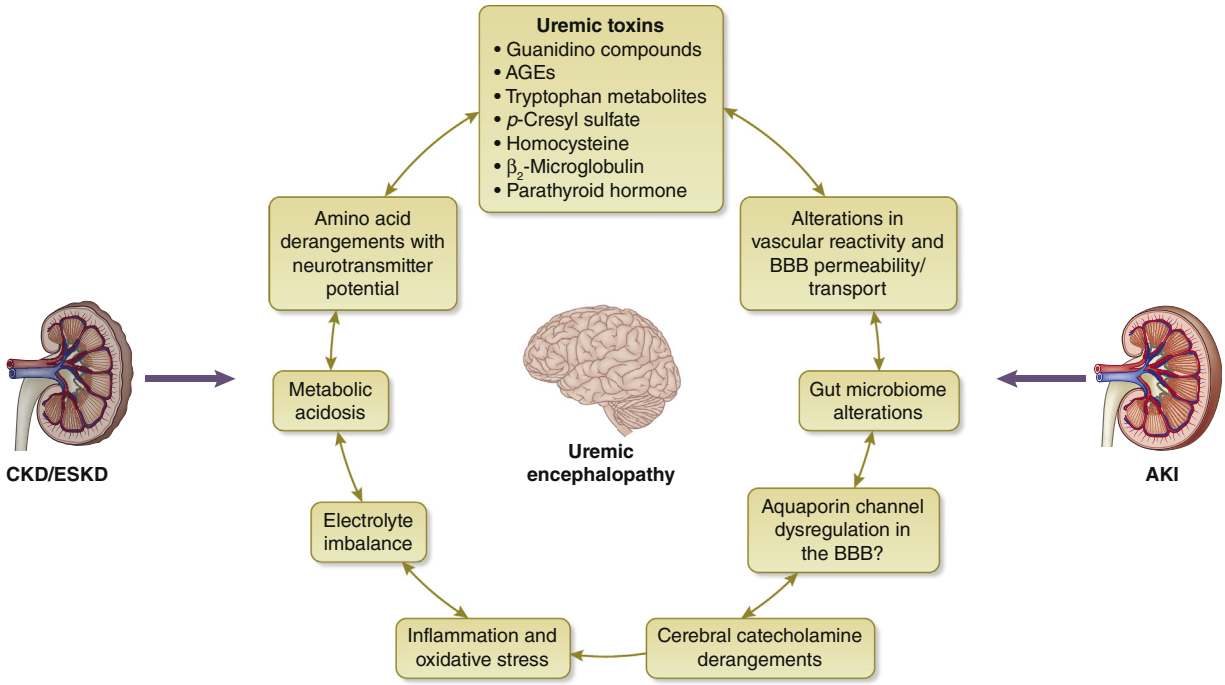

Figure 2 | Potential mechanisms of uremic encephalopathy. The figure illustrates the proposed mechanisms that may contribute to the development of uremic encephalopathy in the setting of advanced chronic kidney disease (CKD) and acute kidney injury (AKI). Various factors that are not directly related to uremia but are worsened by kidney disease may cause neurological complications or cognitive dysfunction. These conditions include diabetes mellitus, hypertension cerebrovascular and cardiovascular diseases, and liver disease. In the acute setting, conditions such as sepsis, trauma, or severe brain hypoperfusion (e.g., due to hypotension) may further aggravate the neurological symptoms and/or the mental state, creating a complex clinical picture with a wide range of differential diagnoses of uremic encephalopathy. AGE, advanced glycation end product; BBB, blood–brain barrier; ESKD, end-stage kidney disease.

Table 3 | Identified uremic neurotoxins

Toxin	Clinical data	Experimental data
Small water-soluble compounds		
Guanidines[a]		X
ADMA	X	
Myoinositol		X
Acrolein		X
Trimethylamine	X	
Protein-bound compounds		
AGEs		X
***p*-Cresyl sulfate**		X
Indoxyl sulfate	X	X
Indole acetic acid		X
Kynurenines		X
Quinolinic acid		X
Homocysteine		X
4-Hydroxyphenylacetic acid	X	
Middle molecules		
β_2-Microglobulin		X
Ghrelin		X
Methionine enkephalin		X
Neuropeptide Y		X
Parathyroid hormone		X

ADMA, asymmetric dimethyl arginine; AGE, advanced glycation end product.
[a]Guanidine, creatinine, guanidinosuccinic acid, methylguanidine, and guanidino acetic acid.
Data modified from Vanholder R, Pletinck A, Schepers E, et al. Biochemical and clinical impact of organic uremic retention solutes: a comprehensive update. *Toxins (Basel).* 2018;10:33.[25]
Bold indicates toxins discussed in detail in the text; normal font indicates that neurotoxic effects have been described but cannot be linked directly to cognition or encephalopathy. All references supporting these data can be found in the section on Uremic toxins of this article.

receptor activation.[41] Another suggested mechanism by which indoxyl sulfate could affect brain function is by inhibiting removal by organic acid transporters of other neurotoxins and neurotransmitters and their metabolites.[42] In an observational study, indoxyl sulfate was negatively associated with cognitive function as assessed using the Mini-Mental State Examination and Cognitive Abilities Screening Instrument. This correlation remained significant after adjustment for confounders.[43]

Indole-3-acetic acid, kynurenines, and quinolinic acid. In an observational targeted metabolome analysis, indole-3-acetic acid was associated with cognitive dysfunction,[44] which however is no indication of causation. Acute injection of another indole, kynurenine, as a precursor of kynurenic acid, impaired cognitive flexibility. This effect was modulated by galantamine, a nicotinic acetylcholine receptor antagonist.[45] Quinolinic acid is a metabolite of kynurenic acid and an acknowledged neurotoxin, exerting its activity through neuroinflammation and alterations of the BBB.[46] Most neurotoxicity studies applied striatal or cerebroventricular injections of quinolinic acid. Although increases in blood levels of quinolinic acid as those observed in CKD cause a rise of concentration in the brain and cerebrospinal fluid (CSF),[47] it remains unclear whether rising blood concentration of quinolinic acid to uremic levels would induce similar functional changes as those observed after local injection.

p-***Cresyl sulfate***. In an experimental study in unilaterally nephrectomized mice, *p*-cresyl sulfate administration caused behavioral disturbances and neurodegeneration involving oxidative stress and inflammation.[48]

Homocysteine. Homocysteine has repeatedly been linked to neurological pathology. Homocysteine was neurotoxic to cultured cortical neurons and astrocytes at concentrations comparable to those in CKD, and this effect was mediated by free radicals and worsened synergistically when quinolinic acid was added.[49] Cerebroventricular administration of homocysteine to rats caused deficiencies in learning capacity and memory.[50] Postnatal administration to rats induced cerebellar damage and decreased Purkinje cell count.[51] Finally, homocysteine worsened brain damage poststroke, via activation of microglia and induction of pro-inflammatory mediators.[52] In some studies, the damaging effects are already seen after 24 to 72 hours.[49,52]

β_2-Microglobulin. β_2-Microglobulin is traditionally considered as a marker of the uremic retention of small peptides (also known as *middle molecules*). However, in a milestone study assessing functional neurological changes during aging in mice, β_2-microglobulin was identified as a pro-aging factor, impairing hippocampal cognitive and reparative function in an age-dependent way.[53] Exogenous β_2-microglobulin injected systemically or locally in the hippocampus deregulated hippocampus-dependent cognitive function and nervous cell regeneration capacity even in young healthy mice. Absence of β_2-microglobulin expression abrogated the age-dependent cognitive decline.[53]

Parathyroid hormone. Hyperparathyroidism is common in kidney disease. In experimental CKD in dogs, calcium in brain gray and white matter was increased more in animals with intact parathyroid glands than in parathyroidectomized dogs whereas encephalographic changes were observed only in animals with intact parathyroids.[54] Also in experimental acute uremia, electroencephalographic changes were observed that could largely be prevented by parathyroidectomy.[55] The administration of parathyroid hormone to dogs with normal kidney function or to parathyroidectomized dogs with AKI caused similar encephalographic changes as in animals with kidney failure and intact parathyroids,[55] pointing to parathyroid hormone as a neurotoxin.

Amino acids

Studies in the 1980s demonstrated profound changes of amino acids with neurotransmitter potential in the CSF and cerebral cortex of patients with kidney insufficiency. These comprised an increase in the glycine/valine ratio and a decrease in the CSF/plasma ratio of branched chain amino acids in patients on hemodialysis as well as an increase in a broad array of amino acids, among which are glutamine and glycine, in both acute and chronic uremic rats.[56,57] The importance of these neurotransmitters has been demonstrated in several nonuremic encephalopathies. Glycine is linked to neonatal and childhood encephalopathies, while in hepatic encephalopathy, similar changes in branched amino acids and glutamate occur as in uremic encephalopathy.[58–61] These amino acids do not conform to the classical

definition of "uremic toxins,"[62] as the data for glycine and glutamate do not unequivocally point to accumulation in CKD while circulating branched chain amino acids are decreased.[63–69]

Metabolic acidosis

Metabolic acidosis is a common feature of uremia. Some uremic neurotoxins, such as indoxyl sulfate, contribute to organic acid load. It is difficult to define the pathophysiological role of acidosis in uremic encephalopathy. Encephalopathy has been noted in states of severe acidosis in the absence of marked uremic retention,[70] but in these non-uremic states the presence of intoxicants may as such generate encephalopathy, and in some cases, correction of acidosis does not improve encephalopathy.[71] However, many cases of encephalopathy associated with acidosis show the lentiform fork sign on MRI, which has also been reported in uremic encephalopathy, even in the absence of acidosis.[18] Thus, an independent link between acidosis and uremic encephalopathy remains speculative and requires further study.

Catecholamines

Studies in the 1980s demonstrated catecholamine depletion in the brain of animals with CKD, in spite of an increased plasma concentration,[72] and this reduction could play a role in the pathophysiology of uremic encephalopathic changes.

Effects of kidney insufficiency on neurotransmitters and brain structure

A study conducted in rats investigated the integrity of the BBB 48 hours after bilateral nephrectomy.[73] Uremic retention solutes were identified in the blood of these animals, and 124 of these solutes were detected in the CSF. When kidney function was normal, the CSF/plasma ratio of 31 of 124 solutes was <25%, pointing to a restriction in diffusion across the BBB. Forty-eight hours after bilateral nephrectomy, solutes accumulated in the plasma and in the CSF. However, the CSF/plasma ratio was reduced for the majority of the animals, showing restriction of diffusion across the BBB, and possibly a partial saturation of transport of some solutes via specific transporters.[73] Thus, it is unclear whether uremia itself induces disruption of the BBB. However, in 2 more gradually developing models of CKD (adenine-rich diet and 5/6 nephrectomy models), uremia increased BBB permeability as assessed by radioisotopes.[41]

The mitochondrial respiratory chain is inhibited by various uremic retention compounds such as indoxyl sulfate, *p*-cresol sulfate, hippurate, and kynurenic acid that can lead to excessive production of reactive oxygen species.[74] This correlates with damage to the CNS due to oxidative stress that has been detected in the hippocampus and prefrontal cortex in a rat model of AKI secondary to ischemia-reperfusion injury.[75]

Water transport in the brain is tightly controlled at the level of the BBB and is largely defined by capillary endothelial cells expressing the specific water channels aquaporin 1 and 11 (AQP1/AQP11) and glial foot processes expressing AQP4.[76] Perturbed water flow via brain AQPs has been implicated in many neurological diseases because in states of brain edema water flow via AQP4 may have a harmful effect.[76] Changes in blood osmolality as seen in uremia can lead to changes in their expression; AQP1 and AQP4 may thus indirectly effect CNS function through changes in cellular volume and intracranial pressure.[77] More research is needed to better understand the changes and impact of AQPs in uremia as well as their possible role in encephalopathic states.

Confounding medical conditions

A number of factors that are not directly related to uremia but are provoked or worsened by kidney disease can cause neurological complications or cognitive dysfunction. This creates a complex situation that can worsen or mimic uremic encephalopathy (Tables 2 and 4).[78–88] Some of these conditions are the well-known causes or comorbidities of CKD, such as diabetes mellitus, hypertension, cardiovascular disease, and liver disease. Likewise, in AKI, conditions such as sepsis, trauma, or severe brain hypoperfusion, for example, due to hypotension, have been linked to neurological alterations.[87,89,90] Finally, CNS intoxicants include not only psychotropic and recreational drugs and direct neurotoxins but also pharmaceutical therapies such as commonly used antibiotics or antifungal drugs.[91–94] The neuropathological potential of these compounds is aggravated by decreases in clearance and protein binding that are associated with kidney disease.[95,96] Understanding the role of these confounding medical conditions is essential in refining the diagnosis and therapy of uremic encephalopathy.

UREMIC ENCEPHALOPATHY IN AKI VERSUS CKD

As kidney clearance is decreased in both CKD and AKI, the process of uremic retention and the potential impact of retained toxins on nervous function may be comparable. In line with this reasoning, CNS disturbances in a rat model of cisplatin-induced AKI were reversed by AST-120, an intestinal sorbent of uremic toxin precursors that decreases their serum concentration.[97] In addition, AKI has been associated with functional and metabolic alterations in brain tissue that are identical to those in CKD,[55,98] as well as the development of clinical uremic encephalopathy,[99,100] and the typical lesions of uremic encephalopathy on brain imaging.[101]

Yet, a number of elements also suggest definite differences in pathophysiology and symptoms. First, the uremic solute retention pattern may differ between AKI and CKD. When intensive care patients with AKI and sepsis were matched for serum creatinine to a group of patients with CKD, the levels of the protein bound solutes indoxyl sulfate and *p*-cresyl sulfate were lower in AKI, possibly owing to differences in intestinal precursor generation.[102] Second, severe experimental ischemic AKI, within 24 hours, led to profound changes in brain morphology and function.[103] This occurred via pro-inflammatory mechanisms, possibly mediated by cytokine release and modifications of the

Table 4| Differential diagnosis of uremic encephalopathy

Diagnosis	Neurological symptoms and signs/ mental status changes	Neuroimaging findings	Other possible features
Hypertensive encephalopathy	• Headache, nausea, irritability, agitation, and visual disturbances; symptoms are generally reversible with blood pressure lowering • Seizures and focal neurological signs: common in PRES[78]	• PRES: bilateral increased signal intensity in white matter, predominantly in the parieto-occipital region (T2/FLAIR-weighted MRI); calcarine and paramedian parts of the occipital lobe usually spared • Hypertensive brainstem encephalopathy: increased signal in white matter in the brainstem (T2/FLAIR-weighted MRI)	• Thrombotic microangiopathy • Retinal hemorrhage/exudate and papilledema • End-organ damage (e.g., myocardial infarction, left ventricular failure, and pulmonary edema) • PRES: hypertension associated with drugs (e.g., calcineurin inhibitors), eclampsia, sepsis, and autoimmune diseases
Thrombotic microangiopathy	• Headache, nausea, irritability, agitation, and visual disturbance; cerebral involvement more common in thrombotic thrombocytopenic purpura than in hemolytic uremic syndrome • Seizures: common • Focal neurological signs: may mimic stroke	• Variable findings: lesions compatible with PRES (most common); subcortical and cortical lesions; ischemic/ hemorrhagic stroke; subdural hematoma[79]	• Thrombocytopenia, hemolytic anemia, and fragmented erythrocytes • AKI and diarrhea more common in hemolytic uremic syndrome associated with Shiga toxin–producing infection
Sepsis-associated encephalopathy	• Hallucinations, agitation, hyperventilation, paratonic rigidity, lethargy, and coma • Seizures and focal neurological signs: 10%–20%[80]	• Variable findings: normal; multiple ischemic lesions; leukoencephalopathy; nonspecific subcortical WMLs in the centrum semiovale[80,81]; lesions associated with PRES	• Encephalopathy early feature of infection, often appearing before other features of sepsis • Critical illness neuromyopathy and fever
HE	• Impaired consciousness (sleep disturbance, lethargy, somnolence, and coma); disturbed personality—behavior (euphoria, depression, anxiety, apathy, and inappropriate behavior); neuromuscular impairment (bradykinesia, asterixis, ataxia, hyperactive deep tendon reflexes, and nystagmus) • Seizures: 2%–33%[82] • Focal neurological signs: may mimic stroke	• Basal ganglia hypersensitivity (not specific for HE) (T1-weighted MRI) • WMLs (T2/FLAIR-weighted MRI) • High ADC in chronic HE; low ADC in acute HE (diffusion weighted-MRI)[83]	• Reduced muscle mass, jaundice, ascites, hyponatremia, and other clinically evident signs of liver failure are usually present • AKI in the presence of hepatorenal syndrome
Post-transplantation encephalopathy	• Diverse symptoms and signs depending on etiology; may range from mild (e.g., confusion and disorientation) to severe (e.g., coma) • Seizures and focal neurological signs: depending on etiology	• Variable possible findings (e.g., enhancing ventriculoencephalitis in *Cytomegalovirus* infection; multiple ring-enhanced lesions with predilection for basal ganglia, thalami, and corticomedullary junction in *Toxoplasma gondii* infection; lesions associated with PRES)	• Depending on etiology (e.g., AKI, thrombotic microangiopathy, gingiva hyperplasia due to calcineurin inhibitor toxicity, gastrointestinal disease, and pneumonitis due to *Cytomegalovirus* infection)
Hyponatremia	• Headache, lethargy, hyporeflexia, hypothermia, reversible ataxia, psychosis, and coma; symptoms depend on the severity and rate of development • ODS: behavioral changes, cranial nerve palsies, progressive weakness, quadriplegia, and locked-in syndrome • Seizures: common in severe hyponatremia • Focal neurological signs: unusual	• Acute hyponatremia (<48 h): cerebral edema • ODS: hyperintense pontine and/or extrapontine lesions (T2-weighted MRI) observed in overly rapid correction of chronic hyponatremia[84]; lesions may not appear until 2 wk after development	• Nausea • Concomitant changes in volume status • Concomitant changes in acid–base status and serum potassium (e.g., due to diarrhea, vomiting, and diuretic therapy) • Dialysis-induced hyponatremia may cause hemolysis and hyperkalemia due to acute hypo-osmolality

(*Continued on following page*)

Table 4 | (Continued) **Differential diagnosis of uremic encephalopathy**

Diagnosis	Neurological symptoms and signs/ mental status changes	Neuroimaging findings	Other possible features
Hypernatremia	• Weakness, lethargy, irritability, hyperreflexia, tremor, chorea, and coma; symptoms depend on the severity and rate of development • Seizures: common in severe hypernatremia • Focal neurological signs: unusual	• Acute hypernatremia (<48 h): symmetric brain shrinkage and compensatory widening of the subdural space; shrinkage can cause hemorrhagic events	• Nausea • Concomitant changes in volume status
Hypocalcemia	• Fatigue, emotional lability, anxiety, depression, and neuromuscular irritability (paresthesia, muscle cramps, carpopedal spasm, laryngospasm, Chvostek sign, and Trousseau sign); symptoms depend on the severity and rate of development • Seizures: common in severe hypercalcemia • Focal neurological signs: unusual	• Basal ganglia calcification (chronic hypocalcemia)	• ECG: prolonged corrected QT interval • Arrythmia, papilledema, and muscular weakness • Often concomitant hypomagnesemia
Hypercalcemia	• Proximal weakness, anxiety, depression, lethargy, coma, and parkinsonism; symptoms depend on the severity and rate of development • Seizures: rare • Focal neurological signs: unusual	—	• ECG: shortening of the corrected QT interval • Bradycardia, muscle weakness, nausea, constipation, peptic ulcer, pancreatitis, polyuria, polydipsia, urinary tract stones, distal renal tubular acidosis, and AKI
Hypomagnesemia	• Neuromuscular hyperexcitability (hyperreflexia, carpopedal spasm, and tremor) and nystagmus; symptoms depend on the severity and rate of development • Seizures: common in severe hypomagnesemia • Focal neurological signs: unusual	—	• ECG: prolonged corrected QT interval and ST segment depression • Ventricular arrythmia and general weakness • Concomitant hypocalcemia and hypokalemia
Hypermagnesemia	• Ataxia, flaccid areflexic paralysis and coma; symptoms depend on the severity and rate of development • Seizures: unusual • Focal neurological signs: fixed dilated pupils	—	• Prolonged atrioventricular conduction, hypotension, muscle paralysis, and respiratory depression • Concomitant advanced CKD is common
Hypophosphatemia	• Irritability, paresthesia, areflexic paralysis, delirium, and coma; may mimic Wernicke encephalopathy • Seizures: common in severe hypophosphatemia • Focal neurological signs: unusual	• May be associated with lesions observed in ODS[85]	• Reduced muscle strength (e.g., diaphragmatic strength, dysphagia, and ileus), decreased myocardial contractility, cardiomyopathy, rhabdomyolysis, and hemolysis
Hypoglycemia	• Tremor, diaphoresis, pallor, anxiety, arousal, paresthesia, dizziness, weakness, confusion, amnesia, and coma • Seizures: common in severe hypoglycemia (<40 mg/dl) • Focal neurological signs: severe hypoglycemia may mimic stroke	• Variable lesions (gray matter lesions [e.g., neostriatum and hippocampi], periventricular WMLs [e.g., internal capsule and splenium of corpus callosum]); low ADC in lesions (T2/diffusion weighted-MRI)[86]	• Palpitations and hunger

Table 4 | (Continued) **Differential diagnosis of uremic encephalopathy**

Diagnosis	Neurological symptoms and signs/ mental status changes	Neuroimaging findings	Other possible features
Hyperosmolar glycemic state/diabetic ketoacidosis	• Blurry vision, mental obtundation, coma, and hemichorea/ hemiballismus (in the hyperosmolar glycemic state) • Seizures: common in severe hyperglycemia • Focal neurological signs: severe hyperglycemia may mimic stroke	• Cerebral edema may be observed in overly rapid correction of plasma glucose and osmolality • Hemichorea/hemiballism: hyperintense lesions in the putamen and/or caudate contralateral to the symptomatic side (T1-weighted MRI)[86]	• Nausea, thirst, polyuria, dehydration, AKI, weight loss, and abdominal pain (more common in diabetic ketoacidosis) • Often associated with major illness (e.g., acute coronary syndrome, cerebrovascular event, and sepsis) • Often concomitant potassium depletion and metabolic acidosis (in diabetic ketoacidosis)
Intradialytic hypotension	• Lightheadedness, vagal symptoms (e.g., yawning, sighing, and hoarseness), and loss of consciousness • Seizures: common in severe hypotension • Focal neurological signs: unusual	• Subcortical WMLs (T2/FLAIR/ diffusion-weighted MRI)[87]	• Acute coronary syndrome, arrythmia, dyspnea, and nonocclusive mesenteric ischemia
Dialysis disequilibrium syndrome	• Acute onset of headache, nausea, disorientation, confusion during or after dialysis subsiding after several hours • Seizures: nowadays rare • Focal neurological signs: unusual	• Diffuse hyperintensity in bilateral subcortical and deep white matter; high ADC in lesions (T2/FLAIR/ diffusion-weighted MRI)[88]	• Nausea and vomiting
Wernicke-Korsakoff syndrome	• Confusion, ataxia, and oculomotor disturbances (bilateral abducens nerve palsy, gaze-evoked nystagmus, and ophthalmoplegia); confabulation; global amnesia; polyneuropathy; coma • Seizures: rare • Focal neurological signs: unusual	• Bilateral and symmetric increased signal intensity in mammillary bodies, medial thalamus, and periaqueductal gray (T2/FLAIR-weighted MRI)	• Malnutrition and regular consumption of alcohol: common

ADC, apparent diffusion coefficient; AKI, acute kidney injury; CKD, chronic kidney disease; FLAIR, fluid-attenuated inversion recovery; ECG, electrocardiogram; HE, hepatic encephalopathy; MRI, magnetic resonance imaging; ODS, osmotic demyelination syndrome; PRES, posterior reversible encephalopathy syndrome; WML, white matter lesion.

BBB.[104–106] These changes are not typical of uremic changes with CKD and may also be etiology dependent. Third, AKI and encephalopathy may be concomitant consequences of the same underlying diseases (see below), like the hemolytic uremic syndrome, malaria, or leptospirosis, and thus make differentiation from true uremic changes nearly impossible.[107–109] Some have also postulated that symptoms (for the same degree of kidney failure) may be more severe with AKI because of less time for accommodation to uremic solute effects on CNS function.[110]

DIFFERENTIAL DIAGNOSIS OF ENCEPHALOPATHY IN KIDNEY FAILURE

Uremic encephalopathy is a diagnosis of exclusion, based mainly on improvement in clinical condition after the initiation of KRT. When considering uremic encephalopathy as an etiology for CNS symptoms, we recommend that patients with delayed, incomplete, or no neurological recovery after the initiation of dialysis, for at least 3 to 5 sessions, should have a careful examination for other possible explanations of their symptoms (Table 4).[78–88] Although the onset and severity of uremic encephalopathy is related to the severity of azotemia, there is a high interpatient variability in CNS symptoms.[111] For example, uremic encephalopathy is less symptomatic in younger patients than in older patients with severe concomitant diseases or with a history of neurological events.[112] This section focuses on conditions that should be considered in the differential diagnosis of any patient with severe kidney failure.

Hypertensive encephalopathy and posterior reversible encephalopathy syndrome are easily confused with uremic encephalopathy because hypertension is a common feature in all 3 conditions. However, these conditions show significant and often rapid improvement as blood pressure comes under control.[112] Thrombotic microangiopathies are commonly associated with significant CNS dysfunction as well as kidney failure. In these cases, treatment of both conditions is imperative and often leads to significant improvement.[79] An

underappreciated syndrome that can be confused with uremic encephalopathy is sepsis-associated encephalopathy.[80,81] This condition that may be cytokine mediated is typified by diffuse brain dysfunction with no evidence of CNS infection or other etiologies of encephalopathy. In addition, sepsis-associated encephalopathy and uremic encephalopathy may coexist, leading to severe degrees of CNS dysfunction.[8] Hepatic encephalopathy is commonly seen in patients with acute liver failure and cirrhosis and can be confused with uremic encephalopathy in the setting of hepatorenal syndrome and AKI.[83,113] In these circumstances, sorting out the contribution of various underlying conditions to encephalopathy is challenging and requires aggressive multidisciplinary care addressing all reversible etiologies. Serum sodium disturbances occur in up to 25% of critically ill patients, and the associated neurological impairments may mimic or worsen uremic encephalopathy.[114] Altered mental state or seizures could also be due to hypoglycemia, which is frequent in patients with diabetes and advanced CKD because of reduced renal insulin clearance, inadequate nutrition, deranged carbohydrate metabolism, and decreased renal gluconeogenesis.[115] In addition, CNS impairment may occur owing to hyperglycemia, especially in the hyperosmolar hyperglycemic state. Wernicke-Korsakoff syndrome due to thiamine deficiency typically manifests with the triad of mental changes, ataxia, and oculomotor disturbances, but other presentations are not uncommon. Thiamine deficiency may be due to malnourishment caused by critical illness or due to adsorption of the vitamin by the hemofilter.[116] Serum thiamine levels may not reflect adequacy at the cellular level, as uremic toxins (e.g., oxythiamine) can inhibit transketolase activity and cause functional thiamine deficiency.[117]

TREATMENT

KRT, most often hemodialysis, aiming at decreasing the concentration of uremic retention solutes is the therapy of choice. Hemodialysis is typically started with low blood (200–300 ml/min) and dialysate (400–600 ml/min) flow rates as well as shorter time periods to minimize the risk of dialysis disequilibrium syndrome and cerebral edema (see below). The cornerstone to mitigate the risk of cerebral edema in patients with uremic encephalopathy is limiting severe reductions in plasma osmolality.[118] Other measures to avoid a too rapid rate of reduction in plasma osmolality include deploying dialyzers with smaller membrane surfaces, prescribing continuous KRT with reduced clearance (e.g., <20 ml/kg/h), and use of dialysate sodium 10 mmol/l higher than the standard concentration.[118,119] Effective solute removal typically leads to improvement in CNS symptoms over several dialysis sessions with further improvement over time when adequate dialysis clearance is obtained. However, it is important to realize that hemodialysis is most effective in removing small water-soluble solutes and thus it may not be surprising that cognitive function may not completely normalize as some uremic retention solutes are not effectively removed. In addition, the discontinuous nature of hemodialysis may lead to insufficient removal of toxins that were accumulated in between dialysis, which may contribute to incomplete cognitive improvement.

Kidney transplantation also effectively reduces the concentrations of a multitude of uremic toxins as demonstrated in 10 recipients of a living kidney transplant.[120] Most changes were observed within 3 days of surgery with reductions in the concentrations of indoxyl sulfate, hippuric acid, and *p*-cresyl sulfate. The study also evaluated cognitive function in 5 domains, including memory, attention, information processing speed, abstract reasoning, and executive function. Compared with patients on maintenance hemodialysis and patients with CKD stage 4 to 5, the transplant group after 3 months improved only in the processing speed domain. Another study investigated the cognitive function of 21 transplant kidney recipients on an average of 8.5 months after the procedure. There was better performance on cognitive and psychomotor tests that assessed processing speed, attention, short-time memory, convergent thinking, and executive functioning.[121] The differing clinical results between these 2 studies could be partially explained because of differences in the time point of the observation period, which was almost 6 months longer in the later study.[121]

Another strategy that reduces blood concentrations of gut-derived uremic toxins that are likely involved in the pathogenesis of uremic encephalopathy is the oral administration of activated charcoal with adsorptive properties.[122] In an *in vitro* experiment using astrocytes exposed to sera of patients with CKD, indoxyl sulfate concentrations led to a dose-dependent increase in the expression of a proinflammatory phenotype. The introduction of the sorbent reduced indoxyl sulfate. Markers of inflammation were also reduced after the intervention.[123] Nevertheless, clinical studies evaluating neurological outcomes with this approach are lacking.[124] This noninvasive strategy could be valuable in palliative care situations or in patients treated by incremental dialysis.[125]

Hemoperfusion is another extracorporeal blood purification technique applied in the treatment of uremic encephalopathy. A study compared 80 patients undergoing maintenance hemodialysis with 78 patients undergoing maintenance hemodialysis plus hemoperfusion with a macroporous sorbent for 2 years. This sorbent promotes the removal of protein-bound uremic toxins by adsorption.[126] The group that underwent hemoperfusion sessions had improvement in sleep quality and an increment in nocturnal melatonin levels; however, concentrations of uremic toxins were not assessed and more data are needed to support use of this therapeutic option.[127]

Other interventions for the patient with uremic encephalopathy include the following: (i) treatment of nutritional deficiencies, (ii) correction of anemia with iron and erythropoietin supplementation, (iii) treatment of hyperparathyroidism, (iv) treatment of metabolic acidosis and other electrolyte imbalances, and (v) review of medications for possible CNS side effects.

DELAYED RECOVERY OF CNS IMPAIRMENT

Delayed cerebral recovery after the initiation of KRT may occur due to dialysis-associated complications, while overly rapid correction of dysnatremia and hyperglycemia could result in osmotic demyelination syndrome or cerebral edema and tailored dialysate solutions can help avoid these problems.[128,129]

Hypophosphatemia, which is common in malnourished critically ill patients and those on prolonged continuous KRT, may need to be corrected with supplements to prevent hypophosphatemia-associated neurological complications.[130] Intradialytic seizures may occur in patients on maintenance anticonvulsant therapy because of dialysis removal of the drug, and higher postdialysis doses may be required to maintain therapeutic serum concentration. Intradialytic hypotension occurs in 30% to 70% of patients receiving intermittent hemodialysis treatments of AKI and 19% to 43% of continuous dialysis treatments.[131] Intradialytic hypotension may lead to ischemic cardiac injury (also known as *myocardial stunning*) as well as reduced cerebral blood flow and cerebral ischemic injury that can manifest as CNS dysfunction.[131,132]

Dialysis disequilibrium syndrome, a rare reaction to the rapid changes in solute concentration occurring during hemodialysis, may be seen at the initiation of dialysis.[133] This is especially the case in patients with severe long-standing uremia. As with uremic encephalopathy, dialysis disequilibrium syndrome is a diagnosis of exclusion with typical clinical features, most notably the onset or worsening of CNS problems during or after hemodialysis. Those may range from nausea, alterations of consciousness, headache, tremor, myoclonus, and seizures and may ultimately lead to death.[134,135] Hypothesized mechanisms include acute dialysis-induced changes in osmolality, with rapid removal of urea leading to a blood–brain urea gradient and resulting cerebral edema as confirmed by MRI.[134,136] The pathophysiology of cerebral edema during hemodialysis remains to be elucidated although overexpression of AQP4 channels in uremia,[137] accompanied by the reduction in plasma urea concentration during hemodialysis, creates an osmotic gradient between plasma and CSF, favoring the influx of water from the blood compartment toward the CSF and ultimately to the astrocytes. Another theory claims that AKI precipitates an increment in plasma osmolality, promptly precipitating the accumulation of organic osmolytes in brain cells. This is supported by an animal model in which AKI caused an increment in plasma osmolality initially reducing brain water in the first 8 hours of the onset of the insult.[138] Nonetheless, after 48 hours brain water content returned to baseline with a parallel increment in total organic osmolyte content in brain cells. At this time point, the abrupt reduction in plasma osmolyte caused by hemodialysis could create a plasma-CSF osmolality gradient and cerebral edema. Increment in organic osmolytes in brain cells was not observed in animals presenting with CKD, suggesting that in chronic uremic states this mechanism might not play a role in hemodialysis-associated cerebral edema.[138]

When brain edema is suspected, the dialysis treatment should be discontinued. If symptoms persist or worsen after treatment interruption, intracranial pressure–lowering therapies are encouraged, such as head-up positioning (15°–30°), sedation, analgesia, and mechanical ventilation to prevent hypercapnia. If needed, mannitol (up to 0.5–1 g/kg every 4–6 hours) or hypertonic saline (7.5% solution, 100 ml every 4–6 hours) can be administered as osmotic agents.[139] Of note, the use of osmotic agents in patients on dialysis can worsen intravascular congestion secondary to fluid shift from the interstitial compartment toward the blood compartment, which may lead to sudden increase in pulmonary and cardiac filling pressures potentially precipitating acute decompensation of heart failure and pulmonary edema. Patients without residual kidney function and with evidence of volume overload and/or heart failure are particularly predisposed to develop such complications. In refractory cases, lumbar drain and invasive CSF diversion to reduce intracranial pressure have been successfully performed.[140]

Lack of improvement in cognitive dysfunction with dialysis may also reflect suboptimal and discontinuous treatment regimens that impair meeting clearance goals. As there is little evidence that the achievement of target Kt/V is sufficient to correct or prevent uremic encephalopathy, in case of suboptimal CNS improvement, higher clearance targets may be required and should be considered.

FUTURE DIRECTIONS

An interesting but as yet insufficiently explored track to unravel the pathophysiology of uremic encephalopathy is the search for a biostatistical association between specific clinical signs or functional scores and solute concentrations by coupling high-throughput analytical methods to clinical databases. One such investigation searched for metabolites associated with uremic cognitive dysfunction. In a study in patients on hemodialysis, plasma samples were analyzed by gas chromatography-mass spectrometry in a discovery study followed by a second analysis in an independent validation cohort. Of the 4 solutes retained after the first analysis (hippurate, phenylacetylglutamine, propyl-hydroxyproline, and 4-hydroxyphenylacetate), only 4-hydroxyphenylacetate stood the validation test.[141] To our knowledge, there are no studies on the neurological impact of 4-hydroxyphenylacetate. However, the infusion in men of a related compound, phenylacetate, used in the treatment of urea cycle enzyme deficiencies and as oncologic therapy, caused confusion, lethargy, somnolence, and nausea.[142,143] These approaches give hope for both identifying uremic retention solutes and correlating concentrations of the solutes with clinically important symptoms. Identification of these solutes can then lead to more directed removal or pharmaceutical strategies with the aim of improving symptoms and outcomes.

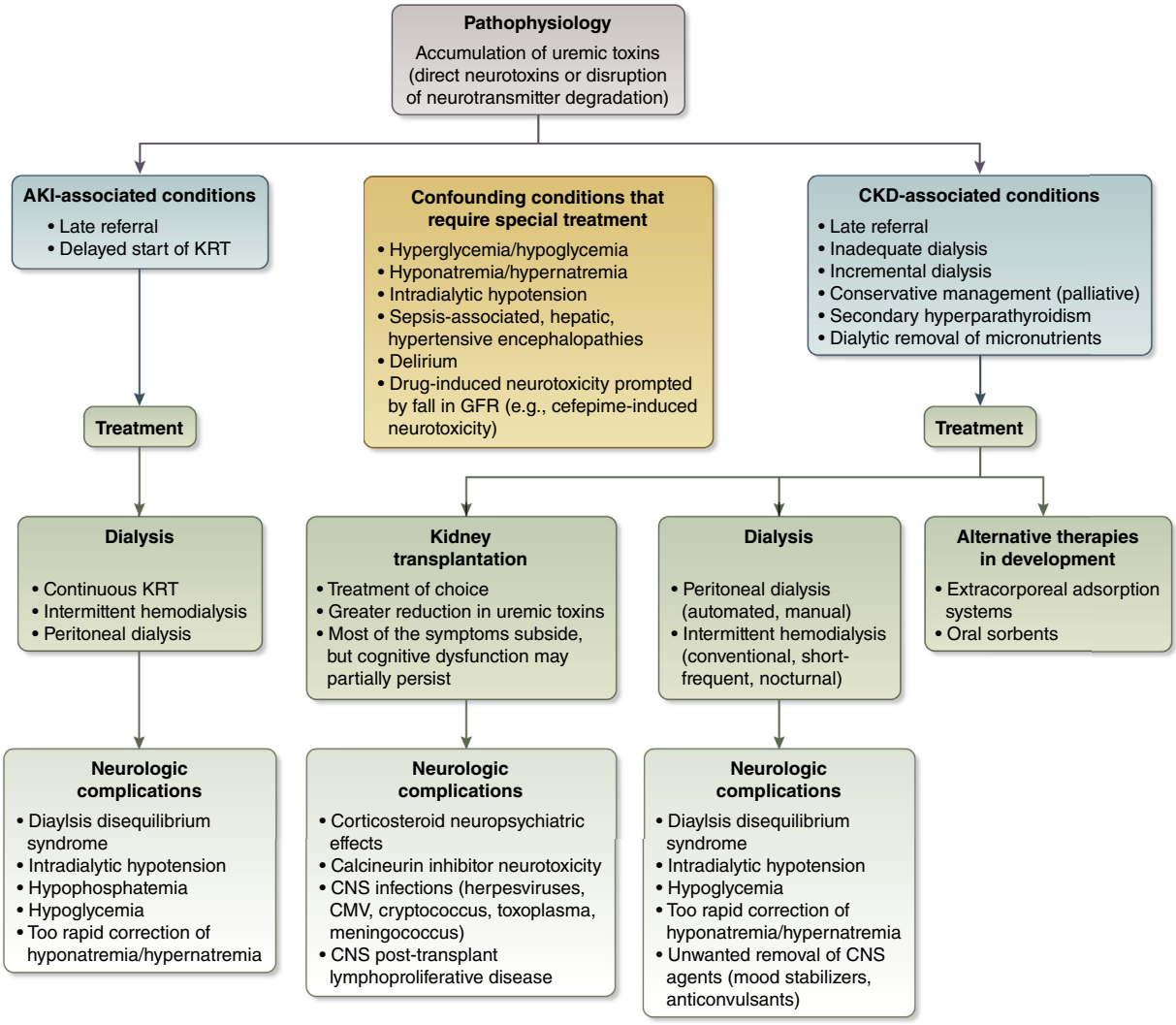

Figure 3 | Summary of key features of uremic encephalopathy. AKI, acute kidney injury; CKD, chronic kidney disease; CMV, cytomegalovirus; CNS, central nervous system; GFR, glomerular filtration rate; KRT, kidney replacement therapy.

Finally, a common characteristic of uremic retention solutes is their difficult removal by conventional dialysis strategies, because of either their molecular weight, protein binding, and/or kinetic behavior. This underscores the potential impact of developing and implementing alternative strategies to decrease uremic toxin concentration, either by novel approaches to extracorporeal removal or by impacting solute concentration in CKD via other mechanisms such as decreasing intestinal generation or preserving kidney function.[144] As many solutes with neurotoxic potential are produced by the intestinal microbiome, influencing this generation process by pre-, pro-, or synbiotics may become a promising therapeutic option for uremic encephalopathy. However, as the intestinal microbiome also produces neuroprotective solutes (e.g., indole and indole-3-propionic acid), such therapies should take care to preserve or restore the balance between beneficial and noxious compounds, rather than decreasing the generation of all metabolites. Of note, studies assessing the clinical impact of therapies influencing the intestinal microbiome (including that on uremic encephalopathy) are to our knowledge nonexistent or of debatable quality.[145]

CONCLUSIONS

Uremic encephalopathy is a complex syndrome seen in patients with severely reduced kidney function. Figure 3 summarizes key elements of the pathophysiology and treatment of this syndrome. The recognition of confounding conditions that can lead to mental status changes and that require specific therapies is critical. The current treatment focuses on the institution of dialysis or transplantation to restore an adequate level of clearance of uremic retention solutes. With this therapy, most patients demonstrate a significant improvement in their mental status and functional capacity.

DISCLOSURE

MHR has received consultant fees from Baxter Healthcare; serves on the data safety monitoring boards of clinical trials sponsored by

Reata, Travere, and AstraZeneca; and is on the editorial board of the *Clinical Journal of the American Society of Nephrology*. TR has received funding for lectures and has been a consultant for or advisory board member of Baxter Healthcare, B. Braun, Contatti Medical (CytoSorbents), Eurofarma, and Jafron. CR has received honoraria for consultation, advisory board participation, or speaker bureau from ASAHI, Bioporto, Biomerieux, Baxter Healthcare, B. Braun, CytoSorbents, Estor, Fresenius Medical Care, General Electric, Jafron, Medtronic, and Toray. RV has received travel support and honoraria from Baxter Healthcare and B. Braun Avitum AG and is an advisor to B. Braun Avitum AG, Baxter Healthcare, Kibow, Jafron, Debiotech, Fresenius Medical Care, and the Dutch Kidney Foundation. FH-S declared no competing interests.

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